Available online on 20.04.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Action of Nanosponges in absorption of bacterial toxins

Prof. Savita Mandan, Yamini Bhadane, Maitreyee Chavan, Umesh Ladha

Department of Pharmaceutics, R.C. Patel Institute of Pharmaceutical Research and Education, Shirpur, Maharashtra

ABSTRACT

Existing detoxification scaffold such as antisera, monoclonal antibodies, small-molecule inhibitors, and molecularly imprinted polymers act by targeting the toxins. Special and specific treatments are required for different diseases. Here we show a biomimetic toxin nanosponge that acts as a toxin decoy in vivo. The nanosponge consists of a polymeric nanoparticle core surrounded by red blood cell membranes. It absorbs membrane-damaging toxins and diverts them away from their cellular targets. Most common toxins in nature, the Pore forming toxins (PFTs), distort cells by forming pores in membranes of the cell and alter their permeability. Apart from their roles in bacterial pathogenesis, PFTs are commonly engaged in venomous attacks by poisonous animals including sea anemones, scorpions, and snakes.

Keywords: Nanosponges, pore forming toxins, absorption.

Article Info: Received 02 Feb 2019; Review Completed 13 April 2019; Accepted 16 April 2019; Available online 20 April 2019

Cite this article as:

Mandan S, Bhadane Y, Chavan M, Ladha U, Action of Nanosponges in absorption of bacterial toxins, Journal of Drug Delivery and Therapeutics. 2018; 8(6-A):144-146

***Address for Correspondence:**

Prof. Savita Mandan, Department of Pharmaceutics, R.C. Patel Institute of Pharmaceutical Research and Education, Shirpur, Maharashtra

Introduction

From the 19th century, the field of medicine has flourished at an incredible rate. The discovery of antibiotics,anticancer drugs, transplant surgeries and various other forms of treatment has allowed humans to survive life-threatening diseases and deforming diseases like Polio, and many else. Yet, there are still diseases that cannot be treated, which has allowed traditional medicine to move into the new direction of using nanomedicine. [1]

An ideal drug therapy is the one which has effective concentration of drug at the target site for a specified period of time in order to prevent or keep to the minimum, general and local side effects. To obtain a desirable therapeutic response, the proper amount of drug should be transported and delivered to the site of action with subsequent controlled release. The distribution of drug to other tissues therefore seems rather unnecessary, wasteful and a potential cause of toxicity. Targeted drug delivery is the delivery of drug to receptor, organ or any part of the body to which one wishes to deliver the drug exclusively.

The first nanoparticles were developed by Peter Paul Speiser in the year, 1960. The nanoparticles were used for targeted drug therapy. This was an impetus for other research developing various carrier systems. At the end of the 20th century, nanoparticles were modified to transport of DNA fragments into cells by using antibodies[2]. Since then there has been a efflux of publications in this area. The publications have increased from 10 articles in 1990 to 1200 articles in 2004, illustrating the snowballing interest in nanomedicine [3].

Difference between Conventional and Nanomedicine

Study states that, 40% of Food and Drug administration (FDA) approved drugs and 90% of the drugs which are under clinical trials are poorly soluble. They have low permeability, rapid clearance by the body and are toxic to the cells of the body [4].

This study has shown that some conventional drugs do not suffice to achieve the desired effect. So, drugs are modified into carrier systems to achieve a better pharmaceutical profile. This is where nanomedicine comes into play. Water insoluble drugs can be encapsulated into the hydrophobic domain of carrier systems such as micelles, polymeric nanoparticles and liposomes. This enables the drug to be carried by a system that has a hydrophilic layer, making drug delivery achievable. Due to the size of these encapsulated drug, it provide an opportunity for targeting tumours via the enhanced permeation and retention effect. The hydrophilic coating makes them less predisposed to clearance by the immune system, leading to longer time in systemic circulation. These carriers can also be modified with ligands or proteins that enable therapeutic targeting. Interestingly the application of nanocarriers extends to diagnostics as these carriers have been modified with imaging contrast agents that selectively

target certain cells and can be visualised using techniques such as magnetic resonance imaging (MRI) [5].

The fields of Nanomedicine have developed ever since the emergence of nanoparticles. These nanoparticles come in various shapes. However, these systems have been chosen for their stealth function as they are coated with particular lipids, as found in the human body making detection by immune cells difficult. These systems include nanocarriers such as liposomes, nanoerythrosomes and micelles [6]. However, they may sound like the perfect solution but even these polymeric nanoparticles are not above recognition and degradation by immune cells [7]. This has led to the development of biomimetic strategies. They are characterised by the ability to bypass the immune system. Biomimetic nanotherapeutics can mimic the cells biological characteristics, as the structure of the system is designed in such a way that the particle has a polymeric core, coated by a lipid membrane. These particles are favored in nanomedicine as they are devised with surface features that are specific for targeting cells or tissues[8]. Current research has shown that biomimicry include particles such as erythrocyte membrane particles with a PLGA core, magnetic core, and PLGA cores enveloped by a white blood cell membranes[9,10,11] .This area is particularly eyed upon as very little research has been conducted on this topic [36].

Nanosponge

Nanosponges is a new concept, made of microscopic particles with few nanometers wide cavities in which a large variety of substances can be encapsulated[12]. Nanosponges are a novel class of hyper-crosslinked polymer based colloidal structures consisting of solid nanoparticles with size range similar to that of the colloidal dispersed phase and nanosized cavities. Well-known examples of nanosponges are titanium-based nanosponges [13].

Nanosponge bead could be of 25µm sized spheres which can have up to 2,50,000 pores and an average internal pore structure equivalent to 10 feet in length and average pore volume of about 1 ml/mg. The drug loading capacity of nanosponges mainly depends on the degree of crystallization [14].

Role in absorption of toxins

Cell targeting virulence factors like toxins of the bacteria illustrate an anitimicrobial approach with potential advantage of increasing the collection of bacterial targets, and lowering of selective pressure for resistance [15,16]. Among various toxins, pore-forming toxins (PFTs) are the most common class of bacterial toxins and make up important bacterial virulence factors [17]. These toxins distort cells by puncturing them by forming pores on their cellular membranes and altering their permeability for any bioactivity [18]. However, the majority of current toxin targeting platforms, such as antisera [19], monoclonal antibodies[20], small-molecule inhibitors [21], and molecularly imprinted polymers [22], depends primarily on structure-specific epitopic binding and special synthesis is required to match specific toxins. As a result, the enormous diversity and numbers of PFTs puts up a serious challenge to derive an effective detoxification platform against bacterial infections. To face this challenge, a unique red blood cell (RBC) membrane-coated nanoparticle system has been recently developed by wrapping a normal RBC membrane onto polymeric nanoparticles (denoted 'nanosponges') for wide range detoxification applications [23, 24]. The term 'nanosponges' explains the unique capability of the RBC membrane-coated nanoparticles for non-specifically 'soaking up' a broad spectrum of PFTs, just like a sponge soaking up water. Unique from existing detoxification approach, these so called nanosponges attack the membrane-disrupting mechanism which is common to PFTs; thereby offering a toxin decoy strategy to absorb various types of their toxins irrespective of their molecular structures [25].

It has been shown that the blocking of the pore-forming α-toxin can reduce the severity of Staphylococcus aureus infections [26], and just like that PFT-targeted strategies have shown therapeutic potential against other pathogens including Escherichia coli [27], Listeria monocytogenes [28], Bacillus anthracis [29], and Streptococcus pneumoniae [30]. Aside from their roles in bacterial pathogenesis, PFTs are commonly employed in venomous attacks by animals including sea anemones, scorpions, and snakes [31]. The pore forming toxins show a diverse molecular structure and over 80 families of PFTs have been identified[37]. Despite these differences, there is functional similarity among these toxins [36].

In toxin Nanosponge, the nano-drug is wrapped with the cell membrane of a natural RBC. This structure minister an ideal mimicry to absorb a wide range of PFTs no matter what their molecular structures is. Simultaneously, the inner polymeric core stabilizes the RBC membrane shell to provide prolonged systemic circulation which is necessary for absorbing toxins in the bloodstream. These nanosponges were prepared by fusing RBC membrane vesicles onto poly(lactic-co-glycolic acid) (PLGA) nanoparticles through an extrusion approach [32]. Under electron microscopy, the resulting nanosponges displayed a core-shell structure of approximately 85 nm in diameter [33]. Nanosponges can be incorporated into a formulated product such as a gel, lotions, cream, ointments, liquid or powder [34].

Conclusion

Nanoparticles' proving advantageous regarding drug targeting, delivery, and release along with their additional potential to combine diagnosis and therapy, is one of the major tools in nanomedicine. The main goals are to improve their stability in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers. The cytotoxicity of nanoparticles or their degradation products remains a major problem, and improvements in biocompatibility obviously are a main concern of future research [35].

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